3
4   UNITED STATES PATENT AND TRADEMARK OFFICE
5   BOARD OF PATENT APPEALS AND INTERFERENCES

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8   Patent Interference 105,592 McK
9   Technology Center 1600

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11
12   **CENTOCOR, INC.**
13   (Inventors: Jill Giles-Komar *et al.*)

14
15   Application 10/912,994,
16   Junior Party,

17
18   v.

19
20   **ABBOTT GmbH & CO., KG,**
21   (Inventors: Jochen Salfeld *et al.*)

22
23   Patent 6,914,128,
24   Senior Party,

25
26
27 *Before:* FRED E. McKELVEY, *Senior Administrative Patent Judge,*
28 and RICHARD E. SCHAFER and SALLY GARDNER LANE,
29 *Administrative Patent Judges.*

30
31 McKELVEY, *Senior Administrative Patent Judge.*

32
33   **MEMORANDUM OPINION**
34   **Decision on Centocor Motion 1 and Abbott Motion 1**

35
36   **A. Why both motions are being considered on the merits**

37   The time: 12 noon.

38   The date: 5 July 2005

1   The event: Issuance of Abbott U.S. Patent, 6,914,128 B1.

2   The place: Abbott's patent department, where excitement was in the

3   air.

4   A research project which began in July of 1993 had finally resulted in

5   a patent.

6   The excitement was short-lived.

7   It turned out that Centocor had a patent application pending claiming

8   the "same patentable invention."

9   Centocor managed to talk the Examiner into recommending and the

10   Board into declaring an interference.

11   Any disinterested observer will immediately appreciate the fact that

12   declaration of the interference put sand in Abbott's patent gears.

13   Looking at the big picture, on previous occasions Abbott and

14   Centocor have been on the same side.

15   An example is a civil action by my state against both of them along

16   with a bunch of others. *Hawaii v. Abbott Laboratories, Inc.*, 469 F. Supp.2d

17   835 (D. Hawaii 2006).

18   While they may have been on the same side in 2006, one gets the

19   impression that lately Abbott and Centocor don't get along when it comes to

20   the market place. *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*,

21   2009 WL 1473431 (E.D. Tex May 27, 2009, as amended May 29, 2009) and

22   2009 WL 938703 (E.D. Tex Apr. 6, 2009).

23   Recent news is not good for Abbott.

24   Apparently, the S.D. Tex. has entered a judgment for Centocor and

25   against Abbott for $1.67 *billion* (not million). See *J&J Wins Record $1.67*

26   *Billion Verdict From Abbott* reported at

27   http://www.bloomberg.com/apps/news?pid=email_en&sid=a0h5zEnztLs0

1   (6 July 2009).

2   We suspect that the Federal Circuit will be asked to look into the

3   judgment.

4   Getting back to the interference, the Board has authority to resolve

5   priority and patentability issues.

6   We have already resolved Abbott Motion 7. Paper 417.

7   No doubt there will be renewed excitement at Abbott over the

8   outcome of Abbott Motion 7.

9   But, it turns out that even if Abbott prevails on priority, Centocor tells

10   us (and Abbott) via Centocor Motion 1 that Abbott's involved patent claims

11   are unpatentable.

12   Abbott tells us (and Centocor) via Abbott Motion 1 that Centocor's

13   involved claim 1 is not patentable over the art.

14   Having prevailed on priority, Abbott says we should *not* get to the

15   issue of patentability because Centocor is *not* the first inventor.

16   By deciding the Abbott priority motion, Abbott reasons that we have

17   answered any question the Examiner may have about issuing an application

18   to Centocor with claims corresponding to what is now a lost count—in other

19   words, the Examiner can now examine the Centocor application.

20   Centocor says that case of unpatentability over the art case has been

21   developed and, we need to go ahead and decide the patentability.

22   At oral argument on 30 June 2009, the pros and cons of deciding the

23   patentability were debated at great length.

24   We agree with Centocor and exercise our discretion (the statute says

25   we "may" consider patentability) and decide Centocor Motion 1.

26   The Examiner cannot get into patentability of the Abbott patent unless

27   a reexamination is requested.

3

1   Abbott is not likely to file a request for reexamination.

2   Centocor does not like the notion of any ex parte and inter partes

3 reexaminations because institution of a reexamination would start the whole

4 process over and delays an eventual ruling on the patentability of Abbott's

5 claims.

6   We have the arguments and evidence of patentability before us.

7   As a result, it makes sense in this particular case to decide

8 patentability.

9   A ruling on patentability—at least in this case—will help Abbott and

10 Centocor executives to plan future business activates.

11   Our decision to look into patentability is consistent with, albeit it not

12 dictated, by *Perkins v. Kwon*, 886 F.2d 325 (Fed. Cir. 1989).

13   We also decide Abbott Motion 1.

14 **B. Introduction**

15   The interference is before a merits panel for consideration of priority

16 and other issues.

17   One of the other issues, is Centocor Motion 1 which seeks judgment

18 against the involved Abbott claims based on alleged unpatentability of those

19 claims under 35 U.S.C. § 103.

20   Centocor has not taken the position that its claims are patentable if the

21 Abbott claims are unpatentable. Accordingly, involved Centocor claims 1,

22 102 and 103 stand or fall with the decision on whether the Abbott claims are

23 unpatentable on the merits under 35 U.S.C. § 103. See 37 C.F.R.

24 § 41.207(c) (2008).

25   Another issue is Abbott Motion 1 which maintains that involved

26 Centocor claim 1 is unpatentable over the art.

4

1   <u>Centocor motion for judgment based on obviousness</u>

2   Centocor filed Centocor Motion 1 for judgment based on alleged

3 unpatentability under 35 U.S.C. § 103 over the prior art. Paper 34.

4   Abbott opposed. Paper 89.

5   Centocor replied. Paper 119.

6   <u>Abbott motion for judgment based on the prior art</u>

7   Abbott filed Abbott Motion 1 for judgment based on alleged

8 unpatentability of involved Centocor claim 1 (but not involved Centocor

9 claims 102 or 103) as being unpatentable over the prior art. Paper 35;

10 see also Paper 36.

11   Centocor opposed. Paper 90.

12   Abbott relied. Paper 121.

13   The motion was deferred to the priority phase. Paper 127.

14   B. <u>Abbreviations</u>

15   The following abbreviations are used in this opinion.

16   **CDR**   Complimentary determining regions (Ex 2040,

17   page 60:16-17)

18   **HBV**   Hepatitis B virus

19   **HIV**   Human immunodeficiency virus

20   **PRC**   Polymerase chain reaction

21   **C. Abbott Motion 1**

22   Abbott Motion 1 maintains that involved Centocor claim 1 is

23 unpatentable under 35 U.S.C. § 102, and alternatively under 35 U.S.C.

24 § 103. Paper 35; see also Paper 36. Abbott Motion 1 does not address

25 involved Centocor claims 102 and 103.

26   We need not spend a lot of time on Abbott Motion 1.

27   It fails to state a claim for relief.

1   A review of the motion immediately establishes that Abbott has not

2 undertaken to prove, or that it has made out, its case on the merits.

3   Abbott's case for relief goes something like this.

4   Abbott's original claim 1 read as follows (Ex 2013, page 145):

5   An isolated human antibody, or an antigen-binding portion

6   thereof, that binds to IL-12, wherein the human antibody is a

7   neutralizing body.

8   The similarity between Abbott's original claim 1 and Centocor claim 1

9 is apparent.

10   Centocor claim 1 reads as follows (Paper 5):

11   An isolated human antibody, or an antigen-binding portion

12   thereof, that binds to human IL-12, wherein said human

13   antibody is a neutralizing antibody.

14   The difference is that Abbott uses the phrase "*the* human antibody"

15 whereas Centocor uses the phrase "*said* human antibody."

16   During pendency of the Abbott non-provisional application which

17 matured into the involved Abbott patent, the Examiner rejected original

18 Abbott claim 1 over the prior art. Ex 2011 (the same exhibit as Ex 1008),

19 page 10.

20   The prior art cited by the Examiner was Trinchieri, U.S. Patent

21 5,811,523 (Ex 2001).

22   Upon filing of a response to the Examiner's rejection, Abbott folded.

23 It cancelled original claim 1. Ex 2012, page 2.

24   In place of original claim 1, Abbott amended claim 8 to recite

25 additional limitations (shown in italics below):

26   An isolated human antibody, or antigen-binding portion thereof,

27   that binds to human IL-12 and *dissociates from human IL-12*

1   *with a K_d of 1 x 10^{-10} M or less and a k_{off} rate constant of*

2   *1 x 10^{-3} s^{-1} or less, as determined by surface plasmon*

3   *resonance.*

4   The portion in italics replaced the "a neutralizing antibody" of original

5 claim 1 and further limits the antibody of original claim 1 to an antibody

6 having a particular degree of neutralization.

7   The Examiner agreed amended claim 8 was allowable and a patent,

8 issued.

9   Claim 8 of the Abbott non-provisional application, upon

10 renumbering—a standard procedure in the USPTO upon allowance of an

11 application—became claim 1 of the Abbott patent.

12   During examination of the Centocor application, the Examiner did not

13 apply the Trinchieri patent—Abbott would say because Centocor did not get

14 around to citing the patent to the Examiner until late in the prosecution.

15   Late citing and related issues involving alleged shenanigans on the

16 part of Centocor have been disposed of via our decision on Abbott Motion 3.

17 Paper 184, rehearing denied, Paper 191.

18   Abbott's proofs of the alleged unpatentability of Centocor claim 1 are

19 based on the Examiner's rejection in the Abbott application—not a rejection

20 of claim 1 of the Centocor application.

21   Abbott's reasoning is that if the Examiner felt Abbott original claim 1

22 was anticipated by Trinchieri, then surely the Examiner has to feel that

23 Centocor claim 1 is unpatentable over Trinchieri.

24   Another way of looking at it is that if Abbott's claim 1 is unpatentable

25 over Trinchieri, then Centocor's claim 1 is also unpatentable over Trinchieri.

26   It is true that Abbott surrendered the subject matter of Abbott original

27 claim 1 upon cancellation of original claim 1. But, we are not evaluating a

1   *recapture* rejection or a *doctrine of equivalents* surrender issue in an

2   infringement context.

3   The initial decision by the Examiner to reject Abbott original claim 1

4   in no way binds Centocor. *Sze v. Bloch*, 59 CCPA 983, 987, 458 F.2d 137,

5   140 (CCPA 1972) (holding during ex parte examination cannot be binding in

6   subsequent inter partes case involving application in which holding was

7   made); *Switzer v. Sockman*, 52 CCPA 759, 333 F.2d 935 (CCPA 1964). If

8   higher authority is needed, see *Keystone Bridge Co. v. Phoenix Iron Co.*,

9   5 Otto (95 U.S.) 274, 279 (1877) (patents are procured *ex parte*; the public is

10   not bound by decision of the Patent Office to issue the patent, but a patentee

11   is). Nor does the Examiner's decision to reject, or not reject, bind us. *Glaxo*

12   *Wellcome Inc. v. Cabilly*, 56 USPQ2d 1983 (Bd. Pat. App. & Int. 2000)

13   We do not know what the Examiner would have done during

14   prosecution of the Abbott non-provisional application had Abbott argued

15   that the rejection of original Abbott claim 1 over Trinchieri was erroneous.

16   As indicated above, Abbott avoided that battle by cancelling claim 1.

17   What we do know is that the Examiner did *not* reject a claim

18   essentially the same as Abbott original claim 1 when it came to prosecution

19   of the Centocor application.

20   Our rules require that a moving party explain why it is entitled to

21   relief. 37 C.F.R. § 41.121(c)(1)(iii) (2008).

22   Abbott does not propose findings or explain *on the merits* why

23   Centocor claim 1 is unpatentable over Trinchieri. What the Examiner did or

24   did not do does not establish for Abbott why involved Centocor claim 1 is

25   unpatentable over Trinchieri.

1   Rather, Abbott tries to back door the matter by saying the Examiner

2   held my claim 1 to be unpatentable over Trinchieri and therefore Centocor's

3   claim 1 has to be unpatentable over Trinchieri.

4   Abbott's position fails to state a claim for relief.

5   On that basis, we deny Abbott Motion 1.

6   **D. Centocor Motion 1**

7   1. Technical background

8   For a tutorial background, we reproduce some of the material set out

9   in our decision on Abbott Motion 7.

10   Interleukin 12—known as IL-12—is a protein made in the body by

11 humans. Paper 405, page 4; Centocor, page 1.

12   In biotechese, IL-12 is referred to as a "cytokine."

13   IL-12 is a useful protein unless—as Yogi Berra would say—it is not a

14 useful protein.

15   IL-12 plays a role in immune response.

16   In other words, when foreign material invades the body, IL-12 might

17 be released as part of the body's immune response.

18   In biotechese, the foreign material is known as an "antigen" (from

19 "antibody generating substances")

20   Unfortunately, IL-12 can be overproduced in the body (or as Abbott

21 states "deregulated"—Paper 405, page 4) and then become what might be

22 referred to as a "self-antigen."

23   Overproduction is not a good thing and is said to lead to such immune

24 diseases as rheumatoid arthritis, psoriasis and Crohn's disease—to name a

25 few. Paper 409, page 1.

26   When overproduction occurs, one way to bring IL-12 back into a

27 "useful" role is to "tie" some of it up so that less IL-12 is available.

9

1   Both parties have discovered that one way to do "tie" up excess IL-12

2   is to bind at least some of it with an antibody.

3   Key to the discovery, is that the antibody be a "human antibody" (as

4   opposed to say a "mouse antibody").

5   Not only does the antibody have to "bind" to IL-12, but it must also

6   "neutralize" IL-12.

7   The diagram below, provided by Centocor (Paper 409, page 2), shows

8   one antigen bound to an antibody.

9

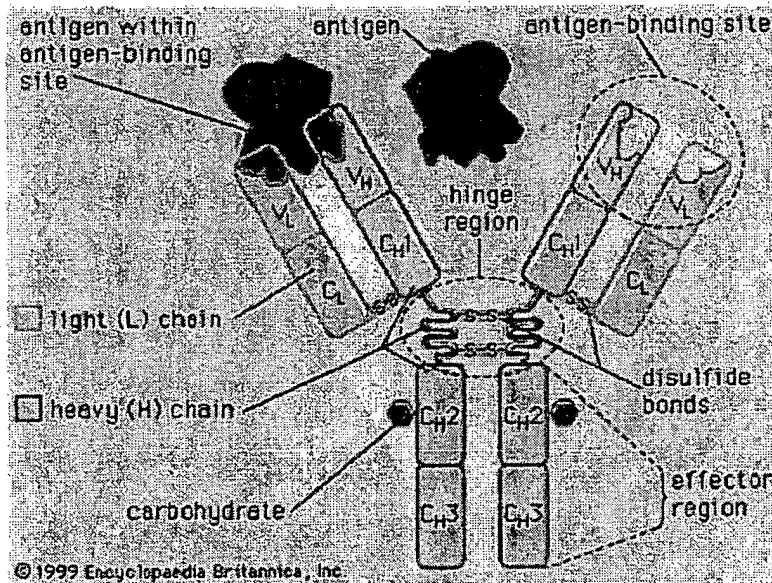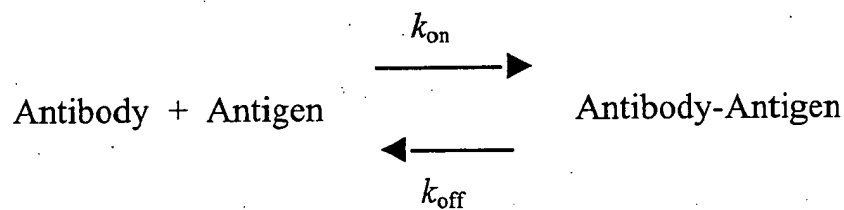10   Fig. 1

11   Schematically depicted is a antigen bound to an antibody

12   As can be seen from the diagram, there are two antigens (the irregular

13   shaped black objects). The antibody is shown as a generally Y-shaped

14   object. One of the antigens (i.e., IL-12) is shown bound to the antibody.

15   The other is shown floating around and is not bound to the antibody.

16   Whether the antigen is sufficiently bound to the antibody depends on

17   the strength of interaction between the antigen and antibody. Paper 409,

page 4. The rate of binding of antigen and antibody at a particular concentration is a constant identified as k_{on}. Another constant (k_{off}) is the rate at which the antigen dissociates from the antibody. Paper 409, page 4. Centocor explains as follows (Paper 409, pages 4-5):

a typical antigen-antibody binding and dissociation can simply be represented as follows:

$$\text{Antibody} + \text{Antigen} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \text{Antibody-Antigen}$$

Equilibrium is reached when the rate at which new antigen-antibody complexes are formed equals the rate at which the antigen-antibody complexes dissociate. At equilibrium:

[Antigen][Antibody]·k_{on} = [Antigen-Antibody] ·k_{off}

K_d is a value that describes the relative relationship of k_{off} and k_{on} when the reaction is at equilibrium.

$$k_{off} / k_{on} = K_d$$

In a footnote (Paper 409, page 5 n.1), Centocor explains:

[Antigen] is a notation for the concentration of Antigen; likewise, the notation [Antibody] refers to the concentration of the Antibody. [Antigen-Antibody] refers to the concentration of the antigen-antibody complex.

The parties tell us that there are various ways to measure antibody-antigen affinities. According to Centocor, one method is using Surface Plasmon Resonance (SPR). Paper 409, pages 5-7. According to Abbott, another method is via Receptor Binding Assay (RBA). Paper 405, pages

11

1 11-12. Yet another method according to Abbott is via PHA Blast

2 Neutralization Assay (PHA). Paper 405, pages 12-13.

3 **E. Centocor's obviousness case--facts**

4 To the extent a sentence is a finding of fact, we believe the finding is

5 supported by a preponderance of the evidence.

6 To the extent a sentence is a conclusion of law, it may be treated as

7 such.

8 1. <u>O'Neil testimony</u>

9 <u>O'Neil's background</u>

10 Centocor's obviousness story emerges from the testimony of

11 Dr. Karyn T. O'Neil (Ex 2015), previously known as K. F. Thompson

12 (Ex 1089, page 239:8-9).

13 O'Neil is an employee of Centocor. Ex 2015. ¶ 1.

14 O'Neil has a 1998 Ph.D. from the University of Pennsylvania.

15 Ex 2015, ¶ 1.

16 O'Neil has been involved with the creation and use of antibody

17 libraries, including phage display libraries, for selection and engineering of

18 antibodies for ten years. Ex 2015, ¶ 2:13-15.

19 The O'Neil declaration was signed in 2008; so "for ten years" means

20 since 1998.

21 During the ten years, O'Neil had extensive experience characterizing

22 and measuring the activity of various proteins, including administering

23 assays measuring IC_{50}. Ex 2015, ¶ 2:16-18.

24 O'Neil says that she is qualified to state the facts and opinions set

25 forth in her testimony. Ex 2015, ¶ 2:18-19.

26 O'Neil has read Abbott Patent 6,914,128 and says she is familiar with

27 its contents. Ex 2015, ¶ 3.

1   O'Neil goes on to describe (1) antibodies, (2) heavy chains, (3) light

2 chains, (4) immunoglobulin diversity, (5) somatic hypermutation and

3 affinity maturation, (6) laboratory production of antibodies, (7) recombinant

4 antibodies, (8) chimeric and humanized antibodies, (9) fully human

5 antibodies, (10) (IL-12, (11) IC_{50} and (12) K_d, k_{on} and k_{off}. Ex 2015, ¶¶ 5-22.

6   O'Neil testified on direct as follows (Ex 2015, ¶ 15):

7   On challenge faced in therapeutic use of monoclonal

8   antibodies is the use of mouse or other rodent antibodies in

9   humans. Although, for example, murine antibodies can have

10   significant structural similarity to human antibodies, there are

11   differences in their sequences and thus their structures. The

12   human immune system recognizes mouse antibodies as foreign,

13   and a process referred to as HAMA (human antibodies to

14   mouse antibodies) rapidly removes them [i.e, the mouse

15   antibodies,] from circulation, causing systemic inflammatory

16   effects. A solution to this problem [i.e., problems caused

17   through use of mouse antibodies in humans,] would be to

18   generate human antibodies directly from humans. However,

19   this [i.e., generation of human antibodies directly from

20   humans,] is not easy, primarily because it is generally not seen

21   as feasible to challenge humans with antigen in order to

22   produce antibody. Furthermore, due to immune tolerance

23   issues, it is not easy to generate human antibodies against

24   human tissue.

25 *See also* Ex 1089, page 199:7-18 (O'Neil cross).

26   O'Neil next walks the Board through various claims in the Abbott

27 patent. Ex 2015, ¶¶ 25-34.

1   There follows a discussion about the prosecution history of the

2   application which matured into the Abbott patent. Ex 2015, ¶¶ 35-40.

3   Prior art relied upon by Centocor

4   O'Neil eventually reaches the prior art which Centocor says renders

5   obvious the subject matter of the involved Abbott claims.

6   The prior art relied upon by Centocor is:

Name	Identification	Date	Exhibit Number
Trinchieri	U.S. Patent 5,811,523	22 Oct 1997	2001

Valiante	145 *Cell. Immunol.*, pages 187-198: Role of the Production of Natural Killer Cell Stimulatory Factor (NKSF/IL-12) in the Ability of B Cell Lines to Stimulate T and NK Cell Proliferation	1992	2002
Chizzonite	147 J. Immunol., pages 1548-56: IL-12: Monoclonal Antibodies Specific for the 40-kDa subunit Block Receptor Binding and Biologic Activity on Activated Human Lymphoblasts	1991	2003
Gately	U.S. Patent 5,780,597	14 Jul 1998	2004
Queen	U.S. Patent 5,530,101	19 Dec 1990	2005
Burton	U.S. Patent 5,652,138	19 July 1994	2006
Curiel	U.S. Patent 5,910,486	6 Jun 1995	2007

Tomlinson	256 J. Mo. Biol., pages 813-17, The Imprint of Somatic Hypermutation on the Repertoire of Human Germline V Genes	1996	2008
Hoogenboom	15 Trends in Biotechnology, pages 62-70	1997	2009

1

2   Abbott does not contest the prior art status of any of the nine prior art

3   references relied upon by Centocor.

4   Basis for alleged unpatentability over the prior art

5   According to Centocor, involved Abbott claims 1-15, 27-40 and 50-64

6   are unpatentable under 35 U.S.C. § 103 over (1) Valiante, (2) Chizzonite

7   and/or (3) Gately further in view of (4) Queen, (5) Burton, (6) Curiel,

8   (7) Tomlinson and (8) Hoogenboom. Paper 34, page 18.

9   Further according to Centocor, involved Abbott claims 1-15, 27-40

10   and 50-64 are unpatentable under 35 U.S.C. § 103 over (1) Trinchieri,

11   (2) Curiel, (3) Tomlinson and (4) Hoogenboom. Paper 34, page 19.

12   Trinchieri

13   According to O'Neil, Trinchieri describes "the complete human IL-12

14   protein." Ex 2015, ¶ 41 (O'Neil direct); Ex 1089, page 133:10 to 134:12

15   (O'Neill cross); Ex 2001, col. 2:27-31 and Figs. 1A-1D.

16   O'Neil testified on direct that Trinchieri claims "a neutralizing human

17   antibody to human IL-12." Ex 2015, page 12:1; Ex 2001, col. 22, claim 5

18   ("The antibody of claim 1 wherein said antibody is a human antibody."). On

1 cross, O'Neil backed off and conceded that Trinchieri claim 5 is not to a

2 "neutralizing" antibody. Ex 1089, page 135:4-13. *See also* Ex 1089,

3 page 150:9-15.

Valiante

5 Valiante is said to describe (1) human IL-12, the p40 and p35 chains

6 of IL-12, (2) recombinant production of IL-12 and (3) *murine* antibodies to

7 human IL-12. Ex 2015, ¶42.

8 The anti-IL-12 "antibody 8.6" described in Valiante contains the

9 subclone "Antibody 8.6.2" said to be described and used in the Examples of

10 the Abbott patent. Ex 2015, ¶ 42:11-13. O'Neil does not have first-hand

11 knowledge of what Abbott *used* in its examples. Neither party attempted to

12 prove what Abbott *used*. From a prior art point of view, what counts is what

13 Valiante *describes*. *Joy Technologies, Inc. v. Manbeck*, 751 F. Supp. 225,

14 233 n.2 (D.C.C. 1990) (Fed. Cir. Judge Bennett—sitting by designation).

15 According to O'Neil, "Antibody 8.6" is shown in Valiante to be a

16 neutralizing antibody by its described effect on reducing the effect of IL-12

17 in cell cultures. Ex 2015, ¶ 42:14-15; Ex 2002, pages 191-195.

18 On cross, O'Neil agreed that Valiante did not describe *human*

19 antibodies to human IL-12. Ex 1089, page 152:5-7.

Chizzonite

21 Chizzonite is said to describe at least (1) human IL-12 and

22 (2) production of *rat* antibodies to human IL-12, and (3) specifically the

23 p40 subunit of IL-12. Ex 2015, ¶ 43; Ex 2003, pages 1548, 1553 and 1554

24 According to O'Neil, Chizzonite characterizes two classes of

25 antibodies: (1) inhibitory antibodies that neutralize IL-12 bioactivity and

26 (2) noninhibitory antibodies that bind to IL-12 without neutralizing

27 bioactivity. Ex 2015, ¶ 43:18-20; Ex 2003, pages 1548-49.

1   Further according to O'Neil, Chizzonite describes neutralizing

2   antibodies that impact IL-12 bioactivity. Ex 2015, ¶ 43:21-22; Ex 2003,

3   page 1553.

4   On cross, O'Neil agreed that Chizzonite does not describe *human*

5   antibodies to human IL-12. Ex 1089, page 154:23-25.

6   Gately

7   Gately is said to describe (1) human IL-12, (2) its p40 and p35 chains

8   and (3) its bioactivity. Ex 2015, ¶ 44; Ex 2004, Examples 2-9.

9   Gately is further said to describe isolation and purification techniques

10   for obtaining IL-12. Ex 2015, ¶ 44:25-26; Ex 2004, Example 1.

11   Gately is still further said to describe specific *non-human* antibodies

12   that are said to neutralize bioactivity of IL-12. Ex 2015, ¶ 44, 26-27;

13   Ex 2004, Example 9 (O'Neil refers to Example 39, but there is no

14   Example 39; we believe she was referring to Example 9).

15   On cross, O'Neil agreed that Gately does not describe human

16   antibodies to human IL-12. Ex 1089, page 157:25 to page 158:3.

17   Queen

18   Queen is said to describe methods for producing humanized

19   antibodies from a non-human donor antibody. Ex 2015, ¶ 45; Ex 2005,

20   col. 11:55-58.

21   Reference is made to chimeric antibodies. We understand a chimeric

22   antibody to be one which contains both (1) human portions and (2) non-

23   human portions. *See, e.g.,* Ex 2015, ¶ 20:26.

24   Queen is said to reveal that non-human antibodies had potential

25   problem when used in humans and therefore human antibodies were

26   desirable. Ex 2015, ¶ 46; Ex 2005, col. 1:33 to col. 2:23.

27   Specifically, Queen states (Ex 2005, col. 1:41-47) (bold in original):

1   Perhaps most importantly, non-human monoclonal

2   antibodies contain substantial stretches of amino acid sequences

3   that will **be-immunogenic when injected into a human**

4   **patient.** Numerous studies have shown that after injection of a

5   foreign antibody, the immune response mounted by a patient

6   can be quite strong, **essentially eliminating the antibody's**

7   **therapeutic utility after an initial treatment.**

8   Putting aside numerous parent applications, Queen was filed in 1990

9   as a continuation-in-part of earlier applications. The earlier applications are

10   not in evidence. In a light most favorable to Centocor, we view Queen as

11   saying that in 1990 the pharmaceutical industry had a reason and motivation

12   to "come up" with a non-chimeric (i.e., fully human) antibody which

13   hopefully would not be "rejected" by the human body after injection.

14   On cross, O'Neil agreed that Queen describes method for producing

15   humanized antibodies from a non-human donor antibody. Ex 1089,

16   page 160:3-7.

17   Nevertheless, O'Neil maintained that Queen might describe a human

18   antibody. Why? On cross, the following occurred (Ex 1089, page 167:4-8):

19   Q. Okay. Do any of the steps referred to in Queen result in a

20   human antibody?

21   A. I think that would depend in the end on the percent

22   homology identity to human antibody genes.

23   A fully human antibody is made from a human source. What O'Neil

24   means by "homology" is that if

25   (1) an antibody is "mostly" (our word) made up of human

26   material, but

19

1   (2) happens to have a minor amount of non-human (say mouse)

2   material where the mouse material sequence looks a lot like

3   (say 80% like) the corresponding human material sequence the

4   mouse sequence replaces, then

5   (3) the antibody is a human antibody.

6 In other words, in O'Neil's opinion a "mostly human antibody" is a "human

7 antibody" even if a minor portion of the mostly human antibody comes

8 from, say, a mouse. We will have more to say about O'Neil's view vis-à-vis

9 what Abbott says in its patent later in this opinion.

10   Burton

11   Burton is said to reveal that as far back as 1991 various techniques

12 had been developed for (1) selecting human antibodies to an antigen and

13 (2) humanizing non-human antibodies—in particular via a "phage display

14 technique. Ex 2015, ¶ 48.

15   According to O'Neil, Burton describes the use of a phage display

16 technique to generate human antibodies to hepatitis B virus (HBV) and HIV.

17 Ex 2015, ¶ 48, page 13:27 through page 14:2.

18   O'Neil then takes us through an analysis of Burton discussing the

19 steps one would take to make human antibody to IL-12 and how use of those

20 steps "will enable selection of higher affinity binders." Ex 2015, ¶¶ 49-53.

21   At the root of O'Neil's analysis is a belief that in March of 1999 all

22 one of ordinary skill in the art would need to do in order to find a human

23 antibody to human IL-12 would be carry out the steps of ¶¶ 50-52 of her

24 declaration until a desired affinity was achieved. Ex 1089, page 195:18

25 through page 196:10.

1   Thus, in O'Neil's opinion, Burton provides the recipe for making

2   human antibody to human IL-12—an objective which would have been

3   predictable.

4   Curiel

5   Curiel is said to show that by 1994 "kits" and reagents for

6   generating phage display libraries were available. Ex 2015, ¶ 54;

7   Ex 2007, col. 7:21-25.

8   Curiel is further said to show that once these kits or methods are used

9   to produce an antibody library on the surface of a display package (e.g., a

10   phage), the antibody library is screened with a protein of interest to identify

11   and isolate packages that express an antibody that binds to the antigen of

12   interest. Ex 2015, ¶ 54:24-27; Ex 2007, col. 7:51-53.

13   Display packages expressing antibodies that bind immobilized

14   antigens can then be selected. Ex 2015, ¶ 54, page 16:1-2.

15   Despite her testimony concerning Curiel "kits," O'Neil indicates that

16   (1) she has no hands-on experience with kits (Ex 1089, page 203:2-3) and

17   (2) she never used "these kits" (Ex 1089, page 204:15-16 and page 207:6-7).

18   Tomlinson

19   Tomlinson is said to describe the mechanism of antibody binding was

20   "well-understood in the art prior to the Abbott patent." Ex 2015, ¶ 58.

21   Tomlinson is also said to describe how it was well known that the

22   antibody contained regions that bound to the antigen through specific

23   protein-protein interactions. Ex 2015, ¶ 58:23-25.

24   An antibody bound to an antigen is shown in Fig. 1 of this opinion.

Hoogenboom

Hoogenboom is said to describe the use and generation of phage display libraries and selection strategies for generating high-affinity antibodies. Ex 2015, ¶ 59; Ex 2009.

As O'Neil explains, techniques described by Hoogenboom are said to allow for human antibodies to be created that bind to a chosen antigen. Ex 2015, ¶ 60.

In addition, the techniques allow for improving binding affinity of these antibodies. Ex 2015, ¶ 60:6.

Additional prior art comment

According to O'Neil, many of the values recited in Abbott's claims are similar to or less stringent than values described in the Abbott patent for prior art antibodies. Ex 2015, ¶ 63.

On cross, O'Neil explains what she means by "many of the values" and "values described" but ultimately agrees that the prior art antibodies said to have been described by Abbott are *not* human antibodies. Ex 1089, page 218:15-17.

Level of skill in the art—O'Neil

On direct, O'Neil testified that in March of 1999 a person having ordinary skill in the art would have a Ph.D. in microbiology "or a similar degree." Ex 2015, ¶ 65.

On cross, O'Neil backtracks and indicates that she does not think it absolutely essential that one have a Ph.D. Ex 1089, page 89:18-20.

Apparently, someone with the experience of a Ph.D. in terms of laboratory skill would be skilled in the art. Ex 1089, page 90:9-12.

In addition, the "person" would have four years of experience making, modifying and testing antibodies. Ex 2015, ¶ 65:2. On cross, O'Neil

1 explains that four years "is about a reasonable timeframe for that, and so that

2 being the first couple of years of your Ph.D. you're probably not doing an

3 enormous amount of hands-on things ..." Ex 1089, page 89:11-18.

4 We have said in past cases that identifying a degree and years of

5 experience is not helpful. *Argyropoulos v. Swarup*, 56 USPQ2d 1795, 1807

6 (Bd. Pat. App. & Int. 2000) (explaining why defining the level of skill in the

7 art in terms of degrees obtained is less helpful than defining it in terms of

8 what such a person would have known and what the person would have been

9 able to do). Abbott's cross-examination of O'Neil more than proves our

10 point.

11 Back to the level of skill, O'Neil tells us that persons of ordinary skill

12 in "this art" keep abreast of the literature and routinely apply scientific

13 discoveries to practical uses. Ex 2015, ¶ 65:3:4.

14 The level of skill "was and is very high." Ex 2015, ¶ 65:5.

15 One skilled in the art would have been very familiar with the

16 techniques for (1) obtaining non-human antibodies for a known antigen,

17 (2) humanizing non-human antibodies and (3) improving the affinity of

18 antibody. Ex 2015, ¶ 65:6-8.

19 One skilled in the art would have known of the desirability of

20 achieving human antibodies with the Abbott claimed values (i.e., K_d and

21 k_{off}). Ex 2015, ¶ 64. How would one skilled in the art obtain the claimed

22 values? By using (1) well-known humanization and affinity maturation

23 methods and phage display selection techniques, (2) generating human

24 antibodies having the claimed values "and/or" (3) improving the affinity of

25 prior art antibodies in order to achieve the claimed values—all said by

26 O'Neil to be "well within" the skill of the art in 1999. Ex 2015, ¶ 64:22-26

1 (direct); Ex 1089, page 219:6 to page 220:22. At this point, one plausibly

2 might wonder if O'Neil forgot that portion of her direct where she states:

3   However, this [i.e., generation of human antibodies directly

4   from humans,] is not easy, primarily because it is generally not

5   seen as feasible to challenge humans with antigen in order to

6   produce antibody. Furthermore, due to immune tolerance

7   issues, it is not easy to generate human antibodies against

8   human tissue.

9 Ex 2015, ¶ 15.

10   Obviousness analysis—O'Neil

11   The problem was to obtain human antibodies with characteristics

12 comparable to prior art non-human anti-IL-12 antibodies. Ex 2015, ¶ 80.

13 When asked on cross, where the problem was identified, O'Neil answered

14 that she did not "know the answer to that." Ex 1089, page 225:19-20.

15   Those skilled in the art had a limited number of available

16 methodologies to obtain the antibody. Ex 2015, ¶ 80:11-12.

17   The person of ordinary skill would have had reason to pursue the

18 small number of methodologies. Ex 2015, ¶ 80:12-17.

19   Quoting from *KSR*, O'Neil appears to assume the role of patent

20 attorney and tells us that obtaining an antibody with the characteristics of

21 Abbott's involved claims was "the product not of innovation but of ordinary

22 skill and common sense." Ex 2015, ¶ 80:17-18.

23   O'Neil was asked whether there would be "a reasonable expectation

24 that the techniques would be successful" (Ex 1089, page 226:6-7). She

25 agreed that there would have been a substantial amount of work. A high

26 amount of work could be achieved says O'Neil depending "on how many

27 people you have working on it." Ex 1089, page 226:23-24. "There [would

1 have been] ... a fairly high expectation of success." Ex 1089, page 227:1.

2 There was a "high probability of success." Ex 1089, page 227:20-21. High

3 probability? Yes. Ex 1089, page 227:22-23. How high? "I would go into it

4 assuming that I was going to be successful, and I think most people at that

5 point in time would also do that." Ex 1089, page 227:25 to page 228:4. So,

6 says O'Neil, "predictability is related to whether it's anticipated that you

7 will be able to identify the antibody that you're looking for." Ex 1089,

8 page 228:15-18.

9   2. Iverson testimony

10   The first—Centocor—to present his case seems right, till another—

11 Abbott—comes forward and questions him. Prov. 18:17. Abbott questions

12 Centocor's case largely through the testimony of Dr. Brent Iverson.

13 Ex 1071.

14   Iverson background

15   Iverson is a Professor in the Department of Chemistry and

16 Biochemistry at the University of Texas. Ex 1071, ¶ 5.

17   He has been an employee of the University of Texas since 1990.

18 Ex 1071, ¶ 4.

19   Iverson was awarded a Ph.D. from California Institute of Technology

20 in chemistry in 1987. Ex 1071, Appendix 1, page 11.

21   While Iverson has worked with antibodies (Ex 1071, ¶ 6), he was not

22 worked with antibodies to human cytokines (Ex 2040, page 15:20-22)

23 (Iverson cross).

24   IL-12 is a human cytokine. Ex 2015, ¶ 18:5 (O'Neil direct).

25   Iverson has worked with catalytic antibodies. Ex 2040,

26 page 16:17-18.

1   Moreover, he says he has "extensive experience" in the field of

2   antibody engineering including development of "novel" antibody

3   engineering technologies and "therapeutic antibodies." Ex 1071, ¶ 8.

4   Level of skill in the art—Iverson

5   In Iverson's opinion, a person having ordinary skill the art would have

6   a Ph.D. in molecular biology or "similar degree" as well as at least three

7   years experience working in the field of antibody engineering technology.

8   Ex 1071, ¶ 7.

9   As becomes apparent, Iverson and O'Neil almost agree, with Iverson

10   requiring only 3 years of experience while O'Neil has a slightly higher 4

11   year experience requirement.

12   We are unable to perceive any significant difference between the

13.   3-year and 4-year requirement.

14   Likewise, we are unable to perceive any significant difference

15   between the degree being in molecular biology (Iverson) or microbiology

16   (O'Neil).

17   The prior art

18   Iverson understands Centocor to bottom its obviousness case on

19   information contained in nine "alleged" prior art references. Ex 1071, ¶ 13.

20   The reason Iverson said "alleged" prior art is that he was wanting to

21   avoid giving an opinion of whether or not the references are legally prior art.

22   Ex 2040, page 51:8-16. Basically, Iverson assumes the references are prior

23   art.

24   As far as Iverson is concerned, the Abbott claims are not to human

25   antibody to human IL-12. Ex 2040, page 51:19 to page 52:2. At first blush

26   it might seem that Iverson is saying that the Abbott claim cover non-human

27   (possibly chimeric) antibody to human IL-12. Close scrutiny will reveal that

1   what Iverson means is that the Abbott claims are to human antibody to

2   human IL-20 with "other essential elements." Ex 2040, page 52:3-10.

3   According to Iverson, none of the nine "alleged" prior art references

4   show all of the essential elements of Abbott's involved claims. Ex 1071,

5   ¶ 14. Iverson recognizes that it is not necessary for a reference to teach all

6   the elements to make out an obviousness case. Ex 2040, page 54:14-18.

7   Iverson had occasion to consider the definition of "human antibody"

8   in the Abbott patent. Ex 1071, ¶ 15.

9   What Iverson found was the following (Ex 2010, col. 26:55 to

10   col. 27:14):

11   The term "human antibody" includes antibodies having variable

12   and constant regions corresponding to human germline

13   immunoglobulin sequences ... [h]owever, the term "human

14   antibody" ... is not intended to include antibodies in which

15   CDR sequences derived from the germline of another

16   mammalian species, such as a mouse, have been grafted onto

17   human framework sequences.

18   In other words, "human antibodies" means human not part human and

19   part something else. A chimeric antibody is not an Abbott "human

20   antibody."

21   According to Iverson, all of the IL-12 references relied on by

22   Centocor refer to research antibody sequences from *non*-humans. Ex 1071,

23   ¶ 16.

24   Valiante and Trinchieri are said to describe a mouse antibody.

25   Ex 1071, ¶ 16.

1   Chizzonite and Gately are said to describe a rat antibody. Ex 1071,

2   ¶ 16. The Iverson direct testimony mentions Trinchieri when it should have

3   referred to Gately, a matter cleared up on cross. Ex 2040, page 57:1-2.

4   According to Iverson, one of ordinary skill in the art in March of 1999

5   would appreciate the scientific distinction between (1) a non-human

6   antibody sequence and (2) a human antibody sequence based on the species

7   origin of the sequences. Ex 1071, ¶ 17.

8   <u>Iverson comment on O'Neil definition of "human antibody"</u>

9   Iverson had an opportunity to comment on the O'Neil definition of

10   "human antibody."

11   Iverson understands, as do we, that the O'Neil definition of human

12   antibody includes any protein at all so long as there is about 80% sequence

13   identity to some human antibody. Ex 1071, ¶¶ 18-19. Iverson refers to

14   O'Neil's cross at Ex 1089, page 13. There O'Neil says that homogenous

15   sequences would be "ok" (our word) provided there is at least about 80

16   percent of the sequences are human. Ex 1089, pages 13:5 and 21-23.

17   In Iverson's view, the O'Neil definition is inconsistent with the general

18   prior art understanding in 1999. A human antibody would be an antibody

19   sequence that originated from a human. Ex 1071, ¶ 22. See also Ex 2040,

20   page 63:9-12:

21   I believe the term "human antibody" refers to an antibody

22   [sequence] that is derived from a human as well as derivatives

23   of that sequence in which changes have been made that enhance

24   properties.

25   Iverson's understanding seems to be consistent with Abbott's definition of

26   "human antibody."

1   Unlike O'Neil, Iverson says "human antibody" is talking about the

2   source not about what percent of the antibody is human. Ex 2040,

3   page 72:13-19. See also Ex 2040, page 73:6-7. "If the sequence derives

4   from a human, it's a human antibody." Ex 2040, page 77:4-5. "If the

5   sequence of the antibody we're talking about is identical to a human

6   antibody sequence derived from a human, it is a human antibody whether or

7   not there happens to be a coincidental sequence correspondence with another

8   species." Ex 2040, page 78:11-15. Lastly, see Ex 2040, page 116:2-7.

9   Iverson also explained that it would be unlikely that a human antibody

10   would have one hundred percent identity to a non-human antibody.

11   Ex 2040, page 115:12-15.

12   Phrase "reasonable expectation of success" and word "therapeutic"

13   What does the phrase "reasonable expectation of success" mean? It

14   appears that it depends on who you ask and the context.

15   Both counsel for the parties and the witnesses mention "expectation of

16   success."

17   There is the "patentese" meaning—the meaning used by patent

18   attorneys, the PTO and the courts—one skilled in the art would reasonably

19   expect success when following the prior art.

20   There is also another meaning—one used by others, such as scientists.

21   For a scientist, success can—but does not necessarily—mean

22   achieving a result after a long arduous investigation.

23   In evaluating testimony of scientists, it may not be a good idea to

24   assume the scientist is using the patentese meaning.

25   There is another word which is used in various ways in this case.

26   The word is "therapeutic."

27   Abbott's claims do not use the word "therapeutic."

1   As a result, Centocor will criticize testimony which attempts to read

2   the word "therapeutic" into the claims.

3   On the other hand, what Abbott would say is the K_d and the k_{off}

4   limitations in a practical way are necessary to obtain a "therapeutic" product.

5   <u>Expectation of success—Iverson's view</u>

6   Iverson recognizes that O'Neil (or at least Centocor—which bases it

7   case on the O'Neil testimony) believes the prior art would have lead one

8   skilled in the art to believe that if you just follow the recipe you would

9   expect success.

10   Iverson testified that if one of ordinary skill in the art were to attempt

11   to isolate a potentially *therapeutic* antibody targeted against IL-12 from a

12   repertoire library, due to the stochastic nature of the underlying process there

13   is no reasonable *expectation of success* in obtaining an antibody sequence

14   having the recited characteristics of the antibody sequence corresponding to

15   Abbott's involved claims. Ex 1071, ¶ 26.

16   Iverson uses the term "therapeutic" to refer to the "characteristics" set

17   out in the Abbott claims. In other words, if the antibody has those

18   characteristics, it is "therapeutic" but if the antibody does not have those

19   characteristics, then it is *not* therapeutic.

20   Iverson addresses "expectation of success." Ex 1071, ¶¶ 26-27.

21   According to Iverson, the O'Neil approach ignores the stochastic

22   nature involved in making the known technology yield the affinity matured

23   human antibody sequence with the characteristics (i.e., K_d and k_{off}) recited in

24   Abbott's involved claims. Ex 1071, ¶ 26.

25   We understand Iverson's reference to "stochastic" to mean that a

26   stochastic process is one whose behavior cannot be precisely determined—

1 whatever result is obtained may be the result of both predictable action and

2 at least one element which is random.

3   . Further according to Iverson, if the processes described in the

4 "alleged" prior art were to be used to attempt to isolate a potentially

5 therapeutic antibody targeted against IL-12 (an antibody with Abbott's

6 claimed characteristics) from a repertoire library not previously

7 immunologically enriched, the "stochastic" nature of the process "means

8 there is no reasonable expectation of success ..." Ex 1071, ¶ 26.

9   Numerous problems are said to have been ignored by O'Neil.

10 Ex 1071, ¶ 27.

11   According to Iverson, in 1999 it was extremely difficult from a

12 technical standpoint to construct highly fertile human sequence repertoire

13 libraries. Ex 1071, ¶ 27.

14   Iverson says there are at least four factors in creating a useful

15 repertoire library with sufficient diversity to obtain an antibody sequence

16 specific for a given target antigen. Ex 1071, ¶ 27.

17   First, the PCR [polymerase chain reaction] amplification of antibody

18 repertoire sequences is complicated by the need to use multiple primers to

19 cover a significant portion of the action repertoire. Ex 1071, ¶ 27.

20   As. a result, PCR efficiency is limited, thereby narrowing cloned

21 sequence diversity. Ex 1027, ¶ 27.

22   A related problem is that it can be difficult to know that all of the

23 appropriate primers are being used to maximize recovery of the antibody

24 sequences from a given natural source. Ex 1071, ¶ 27.

25   Second, isolated antibody sequences must be used to express folded

26 and active antibody proteins in bacteria. Bacteria are the common host for

27 phage display, not mammalian cells. Ex 1017, ¶ 27, page 8.

1   A net result may be that many misfolded and therefore non-functional
2   antibodies limit the functional diversity of the library. Ex 1017, ¶ 27,
3   page 8.

4   Third, cloning heavy and light chain gene sequences independently
5   means that when recombined in a cloned library, any information concerning
6   which heavy chain-light chain combinations are compatible may be lost.
7   Ex 1071, ¶ 27, page 8.

8   A result is that many phage might produce incompatible combinations
9   thereby limiting functional diversity. Ex 1071, ¶ 27, page 8.

10   Fourth, each round of library re-growth favors enrichment of phage
11   that propagate the fastest at the expense of more slowing propagating phage.
12   Ex 1071, ¶ 27, page 8.

13   Enrichment bias can significantly erode library diversity and make it
14   difficult to repeatedly use a given repertoire library. Ex 1071, ¶ 27, page 8.

15   There was considerable cross-examination on what Iverson means by
16   "reasonable expectation of success." It starts at page 90 of Ex 2040.

17   Iverson testified that it means "[i]t's not going to work." Ex 2040,
18   page 90:22.

19   Unsatisfied with that answer, Iverson was asked to be little bit more
20   specific.

21   Iverson explained: "[t]he underlying process is unpredictable."
22   Ex 2040, page 91:7.

23   Counsel stated "so you're saying that because it's unpredictable, it's
24   not going to work?"

25   Iverson further explained: "No. I'm saying it is unpredictable and it's
26   unlikely to work." Ex 2040, page 91:10-11.

27   "Unlikely to work or unlikely to work at all?" asked counsel.

1   Iverson answered: "I mean it's—it's unlikely to work at all."

2   Ex 2040, page 92:5.

3   Counsel came back noting that if it was unlikely to work, "then how

4   do you account for the fact that it has been successfully done prior to 1999

5   by others?" Ex 2040, page 92:16-18.

6   The question demonstrates the problem with using the word "it."

7   Iverson promptly indicated that he was referring to "phase display

8   technology used to isolate antibodies specific to an antigen with no further

9   qualifier." Ex 2040, page 92:19-23.

10   After some back and forth on other matters, Iverson continued to

11   testify: "I still believe that there's no reasonable expectation of success."

12   Ex 2040, page 96:19-20.

13   You mean that it is not likely you would be able to do it asked

14   counsel.

15   Iverson answered: "That is correct." Ex 2040, page 96:25.

16   Iverson was asked about affinity maturation.

17   "Affinity maturation is a process by which the affinity of an antibody

18   ... is improved." Ex 2040, page 99:24-25. The reader familiar with our

19   opinion on Abbott Motion 7 will appreciate that improvement of Joe

20   characteristics from Joe 8 to Joe Y61/Joe J695 involved "affinity

21   maturation."

22   How does one go about improving affinity maturation?

23   Iverson explained that "[t]he underlying process is inherently

24   unpredictable." Ex 2040, page 100:5-6.

25   Obtaining affinities (association constants) greater than 10^9 "was

26   difficult." Ex 2040, page 9.

1   Iverson goes on to say that in 1999 "it is not likely" one would be able

2 to obtain association constants of greater than 10^9. Ex 2040, page 100:15.

3   Counsel asked, "[w]hen you say that affinity maturation is stochastic,

4 you mean it's a random process; is that right?"

5   Iverson noted that "[r]andom can mean a lot of things. I mean it's

6 unpredictable." Ex 2040, page 101:6-7.

7   Later in cross, the following took place (Ex 2040, page 104:3-11)

8 (italics added):

9   Q. Okay. So would—would a person skilled in the art in 1999

10   expect to be able to get an affinity of 10 to the 9th, starting

11   with, let's say, an affinity of 10 to 6th?

12   A. Understanding that this is *unpredictable*, my opinion is that

13   getting an antibody with an affinity of 10 to 9th, inverse molar,

14   association constant, there is a *reasonable expectation* that that

15   could be obtained.

16   "10 to 9th, inverse molar" means 10^{-9} or $1/10^9$.

17   At first blush, it appears that Iverson has contradicted himself. On the

18 one hand, it is unpredictable but on the other hand there is a reasonable

19 expectation of success. What we understand Iverson to be saying is that the

20 field is generally unpredictable, but that ultimately he would have expected

21 that one skilled in the art would have been able to achieve affinities of 10 to

22 the 9th. *Cf.* Ex 2040, page 113:17-20.

23   Achieving 10 to the 9th is one thing, but achieving 10 to the 10th is

24 another thing.

25   As Iverson states (Ex 2040, page 105:17-20):

26   In—in my experience, in my laboratory, it was very difficult to

27   obtain antibodies approaching 10 to the 10th. We had some

1   examples where we were better than 10 to the 9th, but they

2   were rare.

HBV and HIV technology

4   Iverson was of the opinion that O'Neil was of the view that 1992

5   phage display techniques had been used to generate human antibodies to

6   hepatitis B virus and HIV. Ex 1071, ¶ 29 (Iverson direct); Ex 2015, ¶ 48

7   (O'Neil direct).

8   However, in the context of the invention involved in the interference,

9   Iverson believes that O'Neil's view is "misleading" "because it ignores the

10 scientific premise that isolating antibodies to foreign antigen (e.g., HBV and

11 HIV) *is not predictive* for isolating antibodies to self-antigens (e.g., IL-12)."

12 By using the word "misleading" we understand Iverson not to be

13 accusing O'Neil of any improper motive; rather "misleading" means

14 "mistaken."

15 In considering ¶ 29 of Iverson's testimony, Iverson noted during cross

16 that he made an error in citing Burton when he meant Zebedee and another

17 error when he cited Zebedee when he meant Burton. Ex 2040, page 106:23.

18 Iverson agreed that Burton and Zebedee report having isolated

19 antibodies to foreign antigens. Ex 2040, page 108:13-17.

20 However, Iverson explained that "is not predictive" means that "[o]ne

21 does not follows the other." Ex 2040, page 107:16. We understand "[o]ne

22 does not follows the other" to mean isolating antibodies to self-antigens does

23 not predictably follow from isolation of antibodies to foreign antigens.

Abbott's success

25 Despite a back and forth on phage technology and a vigorous cross-

26 examination attack attempting to dislodge Iverson from his

1   "unpredictability" position, counsel for Centocor asked (Ex 2040,

2   page 110:20-21):

3   how to you explain that Abbott was able to obtain such a[n]

4   antibody?

5   In effect, counsel is asking Iverson how was Abbott able to make the

6   claimed invention.

7   The question is not relevant. Section 103 states that "[p]atentability

8   shall not be negatived by the manner in which the invention was made."

9   The question should never have been asked.

10   Responding to the irrelevant question, Iverson noted that he was not

11   involved in the Abbott work and noted according to col. 55:66 *et seq.*,

12   Abbott says in its patent that it achieved its result "in the absence of a phage

13   display selection." Ex 2040, page 111: 9-12.

14   Iverson goes on to say (Ex 2040, page 112:20-23):

15   It is an unpredictable process, because we do not understand

16   ahead of time what changes will produce enhanced affinity. I

17   am unaware, as of 1999, that there were procedures that would

18   reliable product [enhanced affinity].

19   **F. Centocor's obviousness case—discussion**

20   1. Differences

21   In a light most favorable to Centocor, the subject matter of the Abbott

22   claims differs from Trinchieri in that Trinchieri does not describe the K_d and

23   k_{off} limitations in the Abbott claims.

24   Abbott, of course, maintains that in addition Trinchieri does not

25   describe human antibody to human IL-12. The problem with Trinchieri's

26   position is Trinchieri claim 5: "The antibody of claim wherein said antibody

27   is a human antibody." Even if Trinchieri describes a human antibody,

1   O'Neil agrees that it is not a neutralizing human antibody. Ex 1089,

2   page 135:4-13 and page 150:9-15.

3   Other references also differ in that they do not describe human

4   antibodies.

5   The main difference between any one reference and the Abbott

6   claims, however, is that none describe a human IL-12 antibody with Abbott's

7   K_d or k_{off}. In other words, Abbott's claim require a degree of affinity not

8   described in the prior art for any isolated human antibody that binds to

9   IL-12.

10   2. Obviousness

11   Centocor argues that the subject matter of the involved Abbott claims

12   would have been obvious notwithstanding any of these differences.

13   In Centocor's view, this obviousness case boils down to Abbott using

14   known material and processes for their known purpose to achieve an

15   *expected* result.

16   It is the "expected result" which gives us pause—and a considerable

17   pause at that.

18   O'Neil says the subject matter and field are predictable. Iverson says

19   the subject matter and field are *not* predictable. We have a classic—if not to

20   be expected—difference of opinion between well-intended and qualified

21   "experts."

22   Whether technology is predictable or unpredictable is a question of

23   fact. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir.

24   1999).

25   To make a factual finding on unpredictability, we weigh the O'Neil

26   testimony vis-à-vis the Iverson testimony.

1   To the extent that the O'Neil testimony conflicts with that of Iverson,

2   we credit the Iverson testimony over the O'Neil testimony.

3   Our credibility determination is based on a consideration of the O'Neil

4   and Iverson direct and cross-examination testimony, as a whole. In

5   particular, we are more impressed with Iverson's explanation of what would

6   have been expected than O'Neil's explanation. Iverson's definition of human

7   antibody more closely comports with the definition in the Abbott patent.

8   While it does not play a major role in our credibility determination, we note

9   that O'Neil is a Centocor employee whereas Iverson is not an Abbott

10   employee. We believe both witnesses have stated honest opinions based on

11   the evidence each considered and their respective experience. They both

12   believe what they are saying is correct. The witnesses simply have an

13   honest disagreement.

14   As a result of our credibility determination, we find that the

15   technology involved in this case, and in particular the subject matter claimed

16   by Abbott, is generally unpredictable. We also find that one skilled in the

17   art in 1999 would not have had a "reasonable expectation of success" (in the

18   "patentese" sense) based on the prior art relied upon by Centocor.

19   Try as hard as it might, Centocor cannot fit this case squarely within

20   *KSR*.

21   One factor to be considered in an obviousness analysis is whether

22   there is a marketplace demand for the invention. *KSR Int'l Co. v. Teleflex,*

23   *Inc.*, 550 U.S. 398, 418, 127 S. Ct. 1727, 1741 (2007). In this case, we

24   entertain no doubt that there was a market place demand. Stated in other

25   terms, the pharmaceutical industry (and therefore one skilled in the art) was

26   "motivated" to achieve the Abbott invention.

1   Another factor to be considered is whether prior art elements and

2   techniques were being used by the Abbott inventors for their intended

3   purpose. As a general proposition, we think they were.

4   Centocor argues that since techniques known to improve one device

5   (chimeric antibodies) those techniques might be used to improve similar

6   devices (non-chimeric human antibodies) in the same way. *KSR*, 550 U.S. at

7   417, 127 S. Ct. at 1740. *See also In re Sullivan*, 498 F.3d 1345, 1351 (Fed..

8   Cir. 2007) (involving antibodies and rattlesnake venom). We can agree with

9   Centocor that one skilled in the art would have been inclined to use chimeric

10   antibody techniques to make human antibodies.

11   Where the Centocor obviousness case falls apart is when it comes to

12   predictability. As *KSR* notes, to resolve obviousness one has to ask whether

13   the improvement is more than the predicable use of prior art elements

14   according to their established functions. 550 U.S. at 417, 127 S. Ct. 127 at

15   1740. What was unpredictable was an expectation of achieving the claimed

16   affinities. In other words, this is a *not* case where one skilled in the art

17   would have had a reasonable expectation of success as urged by Centocor.

18   *Cf. United States v. Adams*, 383 U.S. 39, 51 (1966) (Adams battery

19   produced a result which was shown to have been unexpected) and *Corona*

20   *Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358, 368-69 (1928) (the

21   catalytic action of an accelerator cannot be forecast by its chemical

22   composition, for such action is not understood and it not known except by

23   actual test).

24   We understand what Centocor, through O'Neil, is trying to say.

25   However, with all due respect to her credentials, we think she fell into a

26   hindsight analysis. Now that "the cat is out of the bag", so to speak, and the

27   Abbott invention is "published" via the Abbott patent, a lot of things become

1 "obvious." Unfortunately for Centocor, the subject matter must have been

2 obvious at the time without the benefit of the Abbott specification.

3 Obviousness is based on prior art which would lead a person skilled in the

4 art to make the claimed invention and reasonably expect success in any

5 endeavor to do so.

<div align="center">Alleged failure of others</div>

7 A so-called secondary factor relevant to an obvious analysis is

8 unsuccessful attempts by others. According to Abbott, others tried to do

9 what Abbott did but gave up. Unfortunately for Abbott, to establish a failure

10 of others Abbott was under a burden to show that the "others" failed

11 notwithstanding actual knowledge of the art relied upon by Centocor.

12 *Toledo Pressed Steel Co. v. Standard Parts, Inc.*, 307 U.S. 350, 356 (1939).

13 Because, Abbott failed to show that the "others" actually knew of the prior

14 art, we decline to accord any weight to Abbott's failure of other proofs and

15 argument.

16 **G. Order**

17 Upon consideration of Centocor Motion 1 and Abbott Motion 1, and

18 for the reasons given, it is

19 ORDERED that Centocor Motion 1 is *denied.*

20 FURTHER ORDERED that Abbott Motion 1 is *denied.*

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